A Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Dapagliflozin as an Add-on to Insulin Therapy in Subjects with Type 1 Diabetes Mellitus * Study two

Published: 04-08-2015
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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON43855

Source
ToetsingOnline

Brief title
MB102-230 (0078/1135)
Dapagliflozin in Patients with Type 1 Diabetes

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Type 1 Diabetes Mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Astra Zeneca

Intervention

Keyword: Dapagliflozin, Insulin Therapy, phase 3, Type 1 Diabetes Mellitus

Outcome measures

Primary outcome

* Change from baseline in HbA1c

Secondary outcome

* Percent change from baseline to Week 24 in total daily insulin dose

* Percent change from baseline to Week 24 in body weight

* Change from baseline to Week 24 in the mean value of 24-hour glucose readings

obtained from CGM

* Change from baseline to Week 24 in mean amplitude of glucose excursion of

24-hour glucose readings obtained from CGM

* Change from baseline to Week 24 in the percent of 24-hour glucose readings

obtained from CGM that falls within the range of > 70 mg/dL and * 180 mg/dL

* Proportion of subjects achieving an HbA1c reduction from baseline to Week 24

visit * 0.5% without severe hypoglycemia events

Study description

Background summary

Type 1 diabetes mellitus (T1DM) is a serious chronic disorder that results in the destruction of insulin-producing pancreatic *-cells. T1DM accounts for approximately 5-10% of all cases of diabetes worldwide, and its incidence continues to increase. Patients with T1DM require lifelong insulin therapy due to their inability to produce endogenous insulin. Insulin requirements in these subjects vary widely and depend on several factors including body weight, activity level, and food intake.
People with T1DM must balance the goal of long-term glycemic control and reduction of complications of the disease with the day-to-day challenges of insulin therapy. The major limiting factor for restoring euglycemia is insulin-related hypoglycemia. Unfortunately, recent data suggest hypoglycaemia remains a common event, with 11.8% of subjects in a clinic registry study experiencing at least one episode of severe hypoglycemia resulting in seizure or loss of consciousness within the past 12 months. The occurrence of severe hypoglycemia did not appear to be related to hemoglobin A1C (HbA1c). However, the risk of recurrent hypoglycemia episodes in T1DM can be related to the degree of glycemic variability, which suggests that reducing the swings in glucose may be of importance in this population.
This Phase 3 study is designed to evaluate the efficacy and safety of dapagliflozin 5 mg and 10 mg as an add-on to insulin therapy when used in subjects with T1DM with inadequate glycemic control.
Dapagliflozin is a stable, competitive, reversible, highly selective, and orally active inhibitor of sodium glucose cotransporter 2 (SGLT-2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin has been recently approved for the treatment of type 2 diabetes mellitus (T2DM).
The mechanism of action (MOA) for dapagliflozin is different from and complementary to the mechanisms of existing medications in other drug classes for T2DM, resulting in the direct, and insulin independent, elimination of glucose by the kidney. Furthermore, as SGLT 2 is almost exclusively expressed in the kidney, the highly selective nature of dapagliflozin minimizes the risk of off-target (ie, non kidney) effects. Therefore, no effects are observed on glucose and/or other carbohydrate transport or absorption in any other organs, including the gut, and no other transporters are affected. As such, dapagliflozin offers an important additional strategy for improving glycemic control as an add-on to insulin in patients with T1DM.

Study objective

Primary Objective
The primary objective of this study is to compare the change from baseline in HbA1c after 24 weeks of double blinded treatment with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin.
Secondary Objectives:
Efficacy
* Compare the percent change from baseline in total daily insulin dose with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double blinded treatment

* Compare the percent change from baseline in body weight with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double blinded treatment
* Compare the change from baseline in the mean value of 24-hour glucose readings obtained from continuous glucose monitoring (CGM) with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
* Compare the change from baseline in mean amplitude of glucose excursion (MAGE) of 24 hour glucose readings obtained from CGM with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
* Compare the change from baseline in the percent of 24-hour glucose readings obtained from CGM that falls within the target range of > 70 mg/dL and * 180 mg/dL with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
* Compare dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin for the proportion of subjects achieving an HbA1c reduction from baseline to Week 24 visit * 0.5% without severe hypoglycemia events

Study design

This trial is a randomized, double-blinded, three-arm, parallel-group, placebo-controlled, multicenter trial to evaluate the efficacy and safety of dapagliflozin, when added to ongoing insulin therapy, in subjects with T1DM and inadequate glycemic control. Approximately 768 subjects will be randomized in this trial. Due to regulatory requirements, approximately 160 subjects (of the 768 subjects) are planned to be be included from Japan.
Potential subjects will be assessed for eligibility criteria at the screening visit. Eligible subjects will enter an 8 week lead in period in order to optimize their diabetes management based on individual subject challenge to glycemic control (including hyperglycemia, hypoglycemia, erratic meal/exercise patterns, as defined by the investigator) and to assess the variability in blood glucose profiles and frequency of hypoglycemic episodes at baseline. No placebo or study medication will be provided during the lead-in period. On Day 1, subjects who meet all the protocol specific enrollment and randomization criteria will be randomized into one of the 3 blinded treatment arms (dapagliflozin 5 mg QD, dapagliflozin 10 mg QD, or placebo QD) in a 1:1:1 ratio. Randomization will be stratified to ensure equal representation across all treatment groups by the following: 1) current use of CGM (this refers to an unblinded/personal device which may already be in use before using the blinded device as part of the study and will be categorized as yes vs no); 2) method of insulin administration at baseline (multiple daily injections ([MDI] vs continuous subcutaneous insulin infusion [CSII]); and 3) baseline A1C * 7.5% and < 9.0% vs * 9.0% and * 10.7%.
Subjects will receive dapagliflozin 5 mg QD, 10 mg QD, or placebo QD for 24 weeks, followed by a 28 week subject- and site-blinded long-term treatment

period. Besides study medications, subjects will be treated with MDI (three or more injections per day of basal and prandial insulin) or CSII. It is recommended that subjects reduce their daily insulin dose by 20% for both basal and bolus insulin after the first dose of study drug on Day 1 to reduce the risk of hypoglycemia, although in some cases it may be necessary to reduce insulin (particularly basal insulin) in advance of study drug administration.
It is at the discretion of the investigator to determine the extent to which to reduce the insulin doses. Throughout the study (from the beginning of the lead-in period to the end of the long term treatment period), insulin dose may be adjusted as deemed appropriate to be consistent with good medical practice according to SMBG readings, local guidance and individual circumstances.
Subjects will be monitored closely with regard to safety parameters, including vital signs, safety laboratory tests, ECGs, and AEs.

Intervention

Subjects who meet all the protocol specific enrollment and randomization criteria will be randomized into one of the 3 blinded treatment arms (dapagliflozin 5 mg QD, dapagliflozin 10 mg QD, or placebo QD) in a 1:1:1 ratio.
Subjects will receive dapagliflozin 5 mg QD, 10 mg QD, or placebo QD for 24 weeks, followed by a 28 week subject- and site-blinded long-term treatment period.

Study burden and risks

See section E9.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Diagnosis of T1DM. In addition, a central laboratory C-peptide < 0.7 ng/mL (0.23 nmol/L) is required
* Ages 18 to 75 years, inclusive
* Insulin use for at least 12 months prior to screening per subject reported or medical records and:
o Method of insulin administration (MDI or CSII) must have been unchanged for at least 3 months prior to screening per subject reported or medical records. Subjects must be taking a total insulin dose of * 0.3 U/kg/day for at least 3 months prior to screening
o If using MDI, the subject must be taking * 3 injections per day
* HbA1c eligibility criteria include:
o Screening Visit: Central laboratory HbA1c * 7.7% and * 11.0%
Note: a one-time repeat HbA1C is allowed for subjects in screening if their initial result is within ± 0.2% of the cut off values
o Week -1 Visit: Central laboratory HbA1c * 7.5 % and * 10.7%
Note: a one-time repeat HbA1C is allowed for subjects in lead-in if their test result is within ± 0.2% of the cut off values
* BMI * 18.5 kg/m2
* Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product
* WOCBP must agree to follow instructions for method(s) of contraception as outlined in the study
* Women must not be breastfeeding

Exclusion criteria

o History of T2DM

Note: subjects with a previous misdiagnosis of T2DM in their medical history must have one of the following in order to be eligible for this trial:
* Positive autoantibodies for GAD65, phosphatase IA-2/IA2*, or zinc transporter 8 (ZnT8) (eg, autoimmune diabetes)
* Fasting c-peptide value below the lower limit of detection performed by the Central Laboratory
o History of maturity onset diabetes of young (MODY)
o Pancreatic surgery, chronic pancreatitis, or other pancreatic disorders that could result in decreased *-cell capacity (eg, pancreatogenous diabetes)
o Previous use of dapagliflozin and/or any other SGLT-2 inhibitors
o Use of insulin-sensitizing agents, such as metformin and/or thiazolidinediones, within 2 months prior to the screening visit
o Use of any GLP-1 receptor agonist within the following timeframe prior to the screening visit:
i) 1 month for once or twice daily administration (eg, liraglutide)
ii) 2 months for once weekly administration
o Any non-insulin, antihyperglycemic agent use within 1 month prior to the Screening visit
o History of diabetes ketoacidosis (DKA) requiring medical intervention (eg, emergency room visit and/or hospitalization) within 1 month prior to the screening visit
o History of hospital admission for glycemic control (either hyperglycemia or hypoglycemia) within 1 month prior to the Screening visit
o Frequent episodes of severe hypoglycemia as defined by more than one episode requiring medical assistance, emergency care (paramedics or emergency room care), and/or glucagon therapy administered by a third-party individual within 1 month prior to the screening visit
o Symptoms of poorly controlled diabetes that would preclude participation in this trial including but not limited to marked polyuria and polydipsia with greater than 10% weight loss during the 3 months prior to screening, or other signs and symptoms
o History of Addison*s disease or chronic adrenal insufficiency
o History of diabetes insipidus

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-09-2016
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dapagliflozin
Generic name:	Dapagliflozin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-08-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-02-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-05-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	09-09-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-09-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-11-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-12-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-05-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-07-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-004599-49-NL
ClinicalTrials.gov	NCT02460978
CCMO	NL53998.028.15